Author's response to reviews

Title: Angiotensin converting enzyme inhibitor therapy in children with Alport syndrome: Effect in urinary albumin, TGF-beta, and nitrite excretion

Authors:
Liora Adler (lweinste@aecom.yu.edu)
Roy Mathew (rom_75@yahoo.com)
Stephen Futterweit (trachtma@lij.edu)
Rachel Frank (rfrank@lij.edu)
Bernard G Gauthier (gauthier@lij.edu)
Kashtan E Clifford (kasht001@maroon.tc.umn.edu)
Howard Trachtman (trachtma@lij.edu)

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PDF covering letter
Response to reviewers’ comments

Review #1 (Dr. Markus Ketteler)
1. I concur that the sum of nitrite + nitrate excretion is reliable and accurate in assessing urinary excretion of NO metabolites under baseline and experimental conditions. However, I have added a reference indicating the primary role of diet in determining nitrate excretion (a fact acknowledged by the reviewer) and the relative constancy of the ratio between nitrite and nitrate excretion in the urine of healthy subjects. Thus, I think it is justified to attribute any changes in urinary nitrite excretion, or lack thereof as in this paper, to renal NO synthesis. I have added this material to the second paragraph on page 7.

2. I have acknowledged in the revised second paragraph on page 7 that the slight decrease in urinary nitrite may have been due to an ACEI-induced decline in GFR. The study did not include a second blood sampling for determination of GFR at the end of ACEI therapy. However, I have added a statement that most children with a normal GFR do not manifest a decrease in renal function after administration of an ACEI for 2 weeks.

3. The authors raise the important point that the lack of efficacy of short-term ACEI in patients with early AS does not rule out a beneficial effect of these drugs later on the disease course. I agree entirely; however, the focus of this paper is only on the response to a 2-week course of ACEI therapy in early AS. Based on the findings, I think it is justified to conclude that at this stage there are no alterations in urinary TGF-β and nitrite excretion and that there is no acutely reversible hemodynamically mediated component to the proteinuria. To clarify this, I have revised the first sentence in the second paragraph on page 7, the last paragraph of the Discussion on page 9, and the Conclusion to state that the results suggest that in early AS there are no alterations in glomerular hemodynamics or acutely reversible ACEI-responsive proteinuria. I have also altered these same sections to clearly state that additional studies are needed to determine precisely when in the course of AS ACEI therapy may be useful to reduce proteinuria and to act as renoprotective agents.

Reviewer #2 (Prof. Giuliana Lama)
1. I have addressed the lack of GFR determinations after ACEI therapy in the above response to reviewer #1.

2. There are no other concerns raised by this reviewer.